PATENT COOPERATION TREATY

PCT 14 DEC 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	24.03.2004
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PU4754WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/20094	25.06.2003	27.06.2002

Applicant
SMITHKLINE BEECHAM CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ullrich, J Tel. +49 89 2399-8048

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 25 MAR 2004
WIPO PCT

Applicant's or agent's file reference PU4754WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/20094	International filing date *(day/month/year)* 25.06.2003	Priority date *(day/month/year)* 27.06.2002
International Patent Classification (IPC) or both national classification and IPC C07D307/26		
Applicant SMITHKLINE BEECHAM CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.12.2003	24.03.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-8510

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/20094

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-36 as originally filed

Claims, Numbers

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

1) Reference is made to the following documents:

D1: WO-A-03024974
D2: WO-A-03022853
D3: WO-A-02060905
D4: MAYER S ET AL: 'Synthesis of Perhydro-Furo[2,3-b]Pyran (and Furan)-3-yl Methanols by Oxygenative Radical Cyclization' TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 30, 23 July 1998 (1998-07-23), pages 8753-8770, XP004124043 ISSN: 0040-4020
D5: GHOSH A K ET AL: 'Nonpeptidal P2 Ligands for HIV Protease Inhibitors: Structure-Based Design, Synthesis, and Biological Evaluation' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 17, 1996, pages 3278-3290, XP002241908 ISSN: 0022-2623 cited in the application
D6: UCHIYAMA M ET AL: 'Stereoselective synthesis of optically active perhydrofuro[2,3-b]furan derivatives' TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 42, no. 28, 9 July 2001 (2001-07-09), pages 4653-4656, XP004245771 ISSN: 0040-4039
D7: GHOSH A K ET AL: 'Synthesis and optical resolution of high affinity P2-ligands for HIV-1 protease inhibitors' TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 36, no. 4, 23 January 1995 (1995-01-23), pages 505-508, XP004028779 ISSN: 0040-4039

1.1) In view of the publication dates of intermediate documents D1-D3, their contents will not be taken into consideration in the present PCT phase.

2) The present application relates to the processes for the preparation of four stereoisomers of (3α, 3αβ, 6αβ)hexahydrofuro[2,3-b]furan-3-ol, which are useful in the preparation of inhibitors of HIV aspartyl protease, and to some intermediates involved in said processes.

3) Novelty (Reference to section V)

3.1) Process claims 1-6, 11, 13, 15 and 18-21

The subject-matter of present claims 1-6, 11, 13, 15 and 18-21 can be considered new in the sense of Article 33(2) PCT because of the different reaction conditions used in

comparison with the prior art teaching.

3.2) Compound claims 7-10, 12, 14 and 16-17

Compounds of formulas (II), (XIX) and (XX) differ from the cited prior art in the R^3 substituent, which is namely a halogen atom.
The compound of formula (III) has not been as well disclosed in any of the cited documents.

Thus the subject-matter of present claims 7-10, 12, 14 and 16-17 meets the requirements of Article 33(2) PCT.

4) Inventive step (Reference to section V)

4.1) Process claims 1-6, 11, 13, 15 and 18-21

The problem to be solved by the present application may be regarded as the provision of a further process for the production of compounds that are useful in the preparation of (3α, 3αβ, 6αβ)hexahydrofuro[2,3-b]furan-3-ol, diastereoisomers and enantiomers thereof.
None of the documents D4-D7 seems to represent a suitable state of the art as the processes therein disclose comprise different reagents, intermediates and reaction conditions.
Thus, the subject-matter of present claims 1-6, 11, 13, 15 and 18-21 appears not to have been suggested by the state of the art and can thus be considered to meet the criteria of Article 33(3) PCT.

4.2) Compound claims 7-10, 12, 14 and 16-17

The subject-matter of present claims 7-10, 12, 14 and 16-17 can also be considered to meet the requirements of Article 33(3) PCT as the mentioned intermediates give a "structural contribution" to the final product and because there is no relevant final-product-related prior art as well as intermediate-related prior art, whose teaching could be used to obtain the desired compound of formula (I) in an analogous process.

5) Unity (Rule 13 PCT)

The independent claims presently on file are considered to meet the unity requirements set forth in Article 13 PCT in view of the intermediates of formulas (II), (III), (XIX) and (XX).

6) Further observations

6.1) The relative term "substantially free" used in the claims and in the description has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).
This expression should be substituted by its definition on page 9.

6.2) The vague and imprecise statement in the description on page 27, lines 15-18, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

6.3) Claim 4 is not clear under Article 6 PCT: it is not in fact apparent how it is possible to arrive at compounds of formula (I) starting from compounds of formula (III).
The reaction conditions are therefore lacking.

6.4) Formula (XIX) of claim 13 is not in line with the same on pages 11-12.